Answer 1:

Bibliographic Information

Dexamethasone inhibits the therapeutic effect of paclitaxel against human ovarian xenograft tumors. Hou, Wen-jing; Liu, Yan. Department of Obstetrics and Gynecology, Changzheng Hospital, Second Military Medical University, Shanghai, Peop. Rep. China. Shanghai Yixue (2008), 31(4), 275-277, C3. Publisher: Shanghai Yixue Bianji Weiyuanhui, CODEN: SIHSD8 ISSN: 0253-9934. Journal written in Chinese. AN 2008:662716 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective To explore the influence of dexamethasone (DEX) on the anti-tumor effect of paclitaxel (PTX) in vivo. Methods Human ovarian xenograft models were established with nude mice and were randomly divided into 4 groups (n = 10), namely, the control group, dexamethasone (1 mg/kg, i.p.) group, paclitaxel (20 mg/kg, iv) group, and a combination (dexamethasone and paclitaxel; dexamethasone was administered 12 h before paclitaxel treatment; drugs were given once every 3 days for 6 cycles) group. The vols. and wt. of tumor mass were detected and the tumor inhibitory rates were calcd. Immunohistochem. assay was used to examine the expression of bcl-xl and cleaved caspase-3 protein. Results The tumor wt. was (1.43 ± 0.13)g in the control group, (1.53 ± 0.16)g in the Dex group, (0.79 ± 0.09)g in the DEX+PTX group, and (0.52 ± 0.06)g in PTX group, with those of the latter 2 groups significantly lower than that of the control group (both P < 0.01). The inhibitory rate of DEX+PTX group was 44.76%, which was significantly lower than that of the PTX group (63.64%). The expression of bcl-xl protein in DEX+PTX group was significantly higher than that of the PTX group (P < 0.00714); the expression of Caspase-3 protein was lower in the Dex+PTX group compared with that in the PTX group (P < 0.00714). Conclusions Pretreatment of human ovarian cell lines SKOV-3 with dexamethasone can inhibit paclitaxel-induced tumor cell apoptosis through inhibiting caspase-3 activity via bcl-xl pathway, thus decreases the therapeutic efficacy of paclitaxel.

Answer 2:

Bibliographic Information

The selective Aurora B kinase inhibitor AZD1152 is a potential new treatment for multiple myeloma. Evans, Robert P.; Naber, Claudia; Steffler, Tara; Checkland, Tamara; Maxwell, Christopher A.; Keats, Jonathan J.; Belch, Andrew R.; Pilarski, Linda M.; Lai, Raymond; Reiman, Tony. Department of Oncology, University of Alberta/Cross Cancer Institute, Edmonton, AB, Can. British Journal of Haematology (2008), 140(3), 295-302. Publisher: Blackwell Publishing Ltd., CODEN: BJHEAL ISSN: 0007-1048. Journal written in English. CAN 148:417468 AN 2008:232751 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Aurora kinases are potential targets for cancer therapy. Previous studies have validated Aurora kinase A as a therapeutic target in multiple myeloma (MM), and have demonstrated in vitro anti-myeloma effects of small mol. Aurora kinase inhibitors that inhibit both Aurora A and B. This study demonstrated that Aurora B kinase was strongly expressed in myeloma cell lines and primary plasma cells. The selective Aurora B inhibitor AZD1152-induced apoptotic death in myeloma cell lines at nanomolar concns., with a cell cycle phenotype consistent with that reported previously for Aurora B inhibition. In some cases, AZD1152 in combination with dexamethasone showed increased anti-myeloma activity compared with the use of either agent alone. AZD1152 was active against sorted CD138+ BM plasma cells from myeloma patients but also, as expected, was toxic to CD138- marrow cells from the same patients. In a murine myeloma xenograft model, AZD1152-inhibited tumor growth at well-tolerated doses and induced cell death in established tumors, with assocd. mild, transient leucopenia. AZD1152 shows promise in these preclin. studies as a novel treatment for MM.

Answer 3:

Bibliographic Information

The Growth-Inhibitory Effects of Dexamethasone on Renal Cell Carcinoma In Vivo and In Vitro. Arai, Yasuyuki; Nonomura,

Norio; Nakai, Yasutomo; Nishimura, Kazou; Oka, Daizo; Shiba, Masahiro; Nakayama, Masashi; Takayama, Hitoshi; Mizutani, Yoichi; Miki, Tsuneharu; Okuyama, Akihiko. Department of Urology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan. Cancer Investigation (2008), 26(1), 35-40. Publisher: Informa Healthcare, CODEN: CINVD7 ISSN: 0735-7907. Journal written in English. CAN 149:70601 AN 2008:25777 CAPLUS

Abstract

Background: Recently, several kinase inhibitors have been reported to exert stronger growth inhibitory effects on metastatic renal cell carcinomas (RCCs) than cytokines such as interferons (IFNs) and interleukin-2 (IL-2). On the contrary, the adverse effects of these drugs are also severe. The aim of this study is to analyze the growth-inhibitory effects of dexamethasone (DEX) on RCC in vivo and in vitro. Methods: The MTT assay was performed using three RCC cell lines, OUR-10, Caki-1, and NC65. OUR-10 cells were s.c. transplanted to the dorsal area of nude mice. The nuclear translocation of glucocorticoid receptor (GR) and NF-κ B was examd. using appropriate antibodies. Concns. of interleukin-6 (IL-6), IL-8, and vascular endothelial cell growth factor (VEGF) in the conditioned media and cytosol were measured by ELISA (ELISA). Results: All three RCC cell lines responded to DEX treatment. The growth of OUR-10 xenografts was significantly inhibited by administration of DEX. GR was translocated into the nucleus on DEX treatment. Intracellular IL-6, as well as IL-6 in the conditioned medium, decreased in OUR-10 cells following treatment with increasing amts. of DEX. Concns. of IL-8 and VEGF in the conditioned medium of OUR-10 and NC65 cells also decreased following DEX treatment, with the inhibition of nuclear translocation of NF-κ B. Conclusion: DEX treatment is a candidate for advanced RCC therapy by inhibiting the activation of NF-κ B and its downstream products such as IL-6, IL-8 and VEGF.

Answer 4:

Bibliographic Information

Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors.
Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. Cancer Biology & Therapy (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 5:

Bibliographic Information

Synthesis and Characterization of Nonsteroidal Glucocorticoid Receptor Modulators for Multiple Myeloma. Hudson, Andrew R.; Roach, Steven L.; Higuchi, Robert I.; Phillips, Dean P.; Bissonnette, Reid P.; Lamph, William W.; Yen, Jean; Li, Yongkai; Adams, Mark E.; Valdez, Lino J.; Vassar, Angie; Cuervo, Catalina; Kallel, E. Adam; Gharbaoui, Catherine J.; Mais, Dale E.; Miner, Jeffrey N.; Marschke, Keith B.; Rungta, Deepa; Negro-Vilar, Andres; Zhi, Lin. Discovery Research, Ligand Pharmaceuticals, Inc., San Diego, CA, USA. Journal of Medicinal Chemistry (2007), 50(19), 4699-4709. Publisher: American Chemical Society, CODEN: JMCMAR ISSN: 0022-2623. Journal written in English. CAN 147:439498 AN 2007:910555 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Structure-activity relationship studies centered around 3'-substituted (Z)-5-(2'-(thienylmethylidene))1,2-dihydro-9-hydroxy-10-methoxy-2,2,4-trimethyl-5H-chromeno[3,4-f]quinolines are described. A series of highly potent and efficacious selective glucocorticoid receptor modulators were identified with in vitro activity comparable to dexamethasone. In vivo evaluation of these compds. utilizing a 28 day mouse tumor xenograft model demonstrated efficacy equal to dexamethasone in the redn. of tumor vol.

Answer 6:

Bibliographic Information

The Bcl-2 Family Protein Inhibitor, ABT-737, Has Substantial Antimyeloma Activity and Shows Synergistic Effect with Dexamethasone and Melphalan. Trudel, Suzanne; Stewart, A. Keith; Li, Zhihua; Shu, Yanjun; Liang, Sheng-Ben; Trieu, Young; Reece, Donna; Paterson, Josh; Wang, Dingyan; Wen, Xiao-Yan. Department of Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, Toronto, Can. Clinical Cancer Research (2007), 13(2, Pt. 1), 621-629. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 146:308645 AN 2007:87080 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: The aim of this study is to investigate the antimyeloma activity of a novel Bcl-2 family inhibitor, ABT-737, in preclin. treatment of multiple myeloma. Exptl. Design: The antimyeloma activity of ABT-737 was evaluated in cultured myeloma cell lines and patient myeloma samples, and in a xenograft mouse myeloma model. Drug combination therapy using ABT-737 with other commonly used myeloma drugs was also investigated. Results: MY5 and JJN3 cell lines exhibited the most sensitivity to ABT-737 with an EC50 of 0.2 and 0.5 μmol/L, resp., with increased cell apoptosis and elevated activated caspase-3. We identified two distinct groups of myeloma patient samples that were either sensitive or resistant to the drug. Four of 15 patient bone marrow samples (27%) were highly sensitive to ABT-737 at doses of 0.25 and 0.5 μmol/L, which eliminated 80% to 90% of myeloma cells as a result of cellular apoptosis 3 days after drug treatment. ABT-737 showed a synergistic effect when combined with dexamethasone or melphalan in inducing myeloma cell death. Furthermore, the dexamethasone-resistant MM1(Dex)R myeloma cell line was highly sensitive to 0.2 μmol/L ABT-737. As detd. by colony assay, little or no detectable toxicity to patient hematol. progenitor cells was obsd. at 1 μmol/L ABT-737. ABT-737 dose dependently suppressed tumor growth in a xenograft MY5 mouse model. Conclusions: These studies show substantial antimyeloma activity of ABT-737 as a single agent or in combination with dexamethasone or melphalan and suggest a rationale for future clin. trials.

Answer 7:

Bibliographic Information

New in vivo results support concerns about harmful effects of cortisone drugs in the treatment of breast cancer. Herr, Ingrid; Buechler, Markus W. Department of General Surgery; Research Group Molecular OncoSurgery, University of Heidelberg, Heidelberg, Germany. Cancer Biology & Therapy (2006), 5(8), 941-942. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal; General Review written in English. CAN 146:514825 AN 2006:1343790 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. The research of Pang et al. (2006) entitled "Dexamethasone decreases xenograft response to paclitaxel through inhibition of tumor cell apoptosis" is reviewed with commentary and refs. Dexamethasone (10-20 mg) is often administered to patients orally or i.v. 30 min to one hour prior to chemotherapy. Thus, a 60-70 kg patient receives between 0.1 and 0.3 mg/kg dexamethasone. While amts. in the range of 0.7-3.6 mg/kg have been used in clin. studies of high dose dexamethasone administration, the Conzen team used dexamethasone at 0.1 mg/kg to be consistent with the common range in cancer treatment. These results raise serious questions about the routine use of dexamethasone in cancer treatment.

Answer 8:

Bibliographic Information

Dexamethasone decreases xenograft response to paclitaxel through inhibition of tumor cell apoptosis. Pang, Diana; Kocherginsky, Masha; Krausz, Thomas; Kim, So-Young; Conzen, Suzanne D. Department of Medicine and Committee on Cancer Biology, University of Chicago, Chicago, IL, USA. Cancer Biology & Therapy (2006), 5(8), 933-940. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 146:309496 AN 2006:1343789 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoid receptor (GR) activation has recently been implicated in the initiation of anti-apoptotic signaling pathways in epithelial cell lines grown in culture. However, the evidence that GR-mediated inhibition of tumor cell apoptosis is the mechanism that diminishes chemotherapy effectiveness in vivo is limited. We therefore initiated a breast cancer xenograft study to examine whether or not pretreatment with glucocorticoids (GCs) decreases tumor response to chemotherapy by inhibiting tumor cell apoptosis. Here we report a significant decrease in paclitaxel-induced apoptosis in xenografts from mice pretreated with dexamethasone (Dex). A significant difference in apoptosis in xenografts from Dex/paclitaxel vs. paclitaxel treated animals was seen eight days following initiation of chemotherapy. Nine days later, mice treated with Dex/paclitaxel had significantly larger tumors compared with those that received paclitaxel alone ($p = 0.032$). Dex pretreatment did not significantly affect tumor cell proliferation rates. Taken together, these results demonstrate that systemic Dex administration results in significantly reduced breast cancer xenograft apoptosis in the context of chemotherapy treatment. We also found that systemic Dex treatment results in upregulation of the anti-apoptotic gene MKP-1 and downregulation of pro-apoptotic Bid and TRAIL genes in tumor cells six hours following Dex treatment. These in vivo gene expression changes correlated with significant inhibition of chemotherapy-induced apoptosis. Interestingly, the decreased chemotherapeutic response of Dex-pretreated tumors persisted for several weeks following treatment. These data suggest that GR-mediated transcriptional regulation of pro- and anti-apoptotic genes contributes to the mechanism through which GCs decrease paclitaxel-induced apoptosis.

Answer 9:

Bibliographic Information

Glucocorticoids Suppress Tumor Angiogenesis and In vivo Growth of Prostate Cancer Cells. Yano, Akihiro; Fujii, Yasuhisa; Iwai, Aki; Kageyama, Yukio; Kihara, Kazunori. Department of Urology, Tokyo Medical and Dental University, Tokyo, Japan. Clinical Cancer Research (2006), 12(10), 3003-3009. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:241939 AN 2006:464146 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: Glucocorticoids, such as prednisone, hydrocortisone, and dexamethasone, are known to produce some clin. benefit for patients with hormone-refractory prostate cancer (HRPC). However, the underlying mechanisms by which glucocorticoids affect HRPC growth are not well established as yet. Here, we hypothesize that the therapeutic effect of glucocorticoids on HRPC can be

attributed to a direct inhibition of angiogenesis through the glucocorticoid receptor by down-regulating two major angiogenic factors, vascular endothelial growth factor (VEGF) and interleukin-8 (IL-8). Exptl. Design: The effects of dexamethasone on VEGF and IL-8 expression and cell proliferation were examd. using DU145, which expresses glucocorticoid receptor. The effects of dexamethasone on DU145 xenografts were detd. by analyzing VEGF and IL-8 gene expression, microvessel d., and tumor vol. Results: Dexamethasone significantly down-regulated VEGF and IL-8 gene expression by 50% ($P < 0.001$) and 89% ($P < 0.001$), resp., and decreased VEGF and IL-8 protein prodn. by 55% ($P < 0.001$) and 74% ($P < 0.001$), resp., under normoxic condition. Similarly, hydrocortisone down-regulated VEGF and IL-8 gene expression. The effects of dexamethasone were completely reversed by the glucocorticoid receptor antagonist RU486. Even under hypoxia-like conditions, dexamethasone inhibited VEGF and IL-8 expression. In DU145 xenografts, dexamethasone significantly decreased tumor vol. and microvessel d. and down-regulated VEGF and IL-8 gene expression, whereas dexamethasone did not affect the in vitro proliferation of the cells. Conclusion: Glucocorticoids suppressed androgen-independent prostate cancer growth possibly due to the inhibition of tumor-assocd. angiogenesis by decreasing VEGF and IL-8 prodn. directly through glucocorticoid receptor in vivo.

Answer 10:

Bibliographic Information

Corticosteroid co-treatment induces resistance to chemotherapy in surgical resections, xenografts, and established cell lines of pancreatic cancer. Zhang, Chengwen; Kolb, Armin; Buechler, Peter; Cato, Andrew C. B.; Mattern, Juergen; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Buechler, Markus W.; Friess, Helmut; Herr, Ingrid. Research Group Molecular Urooncology, German Cancer Research Center, Heidelberg, Germany. BMC Cancer (2006), 6 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. http://www.biomedcentral.com/content/pdf/1471-2407-6-61.pdf Journal; Online Computer File written in English. CAN 144:425939 AN 2006:314605 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Chemotherapy for pancreatic carcinoma often has severe side effects that limit its efficacy. The glucocorticoid (GC) dexamethasone (DEX) is frequently used as co-treatment to prevent side effects of chemotherapy such as nausea, for palliative purposes and to treat allergic reactions. While the potent pro-apoptotic properties and the supportive effects of GCs to tumor therapy in lymphoid cells are well studied, the impact of GCs to cytotoxic treatment of pancreatic carcinoma is unknown. Methods: A prospective study of DEX-mediated resistance was performed using a pancreatic carcinoma xenografted to nude mice, 20 surgical resections and 10 established pancreatic carcinoma cell lines. Anti-apoptotic signaling in response to DEX was examd. by Western blot anal. Results: In vitro, DEX inhibited drug-induced apoptosis and promoted the growth in all of 10 examd. malignant cells. Ex vivo, DEX used in physiol. concns. significantly prevented the cytotoxic effect of gemcitabine and cisplatin in 18 of 20 freshly isolated cell lines from resected pancreatic tumors. No correlation with age, gender, histol., TNM and induction of therapy resistance by DEX co-treatment could be detected. In vivo, DEX totally prevented cytotoxicity of chemotherapy to pancreatic carcinoma cells xenografted to nude mice. Mechanistically, DEX upregulated pro-survival factors and anti-apoptotic genes in established pancreatic carcinoma cells. Conclusions: These data show that DEX induces therapy resistance in pancreatic carcinoma cells and raise the question whether GC-mediated protection of tumor cells from cancer therapy may be dangerous for patients.

Answer 11:

Bibliographic Information

Glucocorticoid-mediated inhibition of chemotherapy in ovarian carcinomas. Zhang, Chengwen; Marme, Alexander; Wenger, Till; Gutwein, Paul; Edler, Lutz; Rittgen, Werner; Debatin, Klaus-Michael; Altevogt, Peter; Mattern, Juergen; Herr, Ingrid. Molecular Urooncology, German Cancer Research Center, Heidelberg, Germany. International Journal of Oncology (2006), 28(2), 551-558. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 145:95902 AN 2006:150417 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The glucocorticoid dexamethasone is frequently used as a co-treatment in cytotoxic cancer therapy, e.g. to prevent nausea, to protect normal tissue or for other reasons. While the potent pro-apoptotic properties and supportive effects of glucocorticoids to tumor therapy in lymphoid cells are well studied, the impact on the cytotoxic treatment of ovarian carcinoma is unknown. We tested apoptosis-induction, viability, tumor growth and protein expression using established cell lines, primary cell lines freshly isolated from patient material and a xenograft on nude mice. We found a general induction of resistance toward cytotoxic therapy by DEX-co-treatment in most of the examd. ovarian cancer cells treated in vitro, ex vivo or in vivo. Resistance occurred independently of cell d. and was found at peak plasma levels of dexamethasone and below. Mechanistically, the dexamethasone-induced expression of survival genes may be involved in the resistance. These data show that glucocorticoid-induced resistance is common in ovarian carcinomas implicating that the use of glucocorticoids may be harmful for cancer patients.

Answer 12:

Bibliographic Information

PC cell-derived growth factor confers resistance to dexamethasone and promotes tumorigenesis in human multiple myeloma. Wang, Wengang; Hayashi, Jun; Serrero, Ginette. Department of Pharmaceutical Sciences, University of Maryland School of Pharmacy, USA. Clinical Cancer Research (2006), 12(1), 49-56. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:343981 AN 2006:12588 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: We have shown previously that the 88 kDa glycoprotein PC cell-derived growth factor (PCDGF/GP88) is expressed and acts as an autocrine growth factor in human multiple myeloma cells. The present study investigates whether PCDGF/GP88 expression in multiple myeloma cells leads to the development of resistance to dexamethasone, a conventional drug for multiple myeloma patients. Exptl. Design: PCDGF functions and signaling pathways in dexamethasone-induced apoptosis were studied using a representative dexamethasone-sensitive multiple myeloma cell line ARP-1. The effect of PCDGF/GP88 was further confirmed in PCDGF/GP88-overexpressed ARP-1 cells. Results: Dexamethasone inhibits cell growth and induces apoptosis in a time- and dose-dependent fashion. Exogenous addn. of PCDGF/GP88 to the ARP-1 cells prevented dexamethasone-induced apoptosis as examd. by flow cytometry anal. and poly(ADP-ribose)polymerase cleavage assay. Signaling studies showed that mitogen-activated protein kinase, phosphatidylinositol 3-kinase, and nuclear factor-κB were involved in the antiapoptotic effect of PCDGF/GP88. Overexpression of PCDGF/GP88 in ARP-1 cells rendered the cells refractory to dexamethasone-mediated apoptosis, enhanced their ability to form colonies in soft agar, and to form tumors in vivo without any change in glucocorticoid receptor expression and function. Conclusion: These data suggest that expression of PCDGF/GP88 confers resistance to dexamethasone and increase tumorigenesis of multiple myeloma cells in mouse xenografts. Our data here also raises the possibility of PCDGF/GP88 as a potential therapeutic target for dexamethasone-resistant multiple myeloma.

Answer 13:

Bibliographic Information

Pretreatment with dexamethasone increases antitumor activity of carboplatin and gemcitabine in mice bearing human cancer Xenografts: in vivo activity, pharmacokinetics, and clinical implications for cancer chemotherapy. Wang, Hui; Li, Mao; Rinehart, John J.; Zhang, Ruiwen. Department of Pharmacology and Toxicology, Division of Clinical Pharmacology, University of Alabama at Birmingham, Birmingham, AL, USA. Clinical Cancer Research (2004), 10(5), 1633-1644. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:307750 AN 2004:194636 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The present study was undertaken to det. the effects of dexamethasone (DEX) pretreatment on antitumor activity and pharmacokinetics of the cancer chemotherapeutic agents carboplatin and gemcitabine. Antitumor activities of carboplatin and

gemcitabine with or without DEX pretreatment were detd. in six murine-human cancer xenograft models, including cancers of colon (LS174T), lung (A549 and H1299), and breast (MCF-7 and MDA-MB-468) and glioma (U87-MG). Effects of DEX on plasma and tissue pharmacokinetics of carboplatin and gemcitabine were also detd. by using the LS174T, A549, and H1299 models. Although DEX alone showed minimal antitumor activity, DEX pretreatment significantly increased the efficacy of carboplatin, gemcitabine, or a combination of both drugs by 2-4-fold in all xenograft models tested. Without DEX treatment, the tumor exposure to carboplatin, measured by the area under the curve, was markedly lower than normal tissues. However, DEX pretreatment significantly increased tumor carboplatin levels, including 200% increase in area under the curve, 100% increase in max. concn., and 160% decrease in clearance. DEX pretreatment similarly increased gemcitabine uptake in tumors. .To our knowledge, this is the first report that DEX significantly enhances the antitumor activity of carboplatin and gemcitabine and increases their accumulation in tumors. These results provide a basis for further evaluation of DEX as a chemosensitizer in patients.

Answer 14:

Bibliographic Information

Rituximab, cyclophosphamide, dexamethasone (RCD) regimen induces cure in a WSU-WM xenograft model and a partial remission in a previously treated Waldenstrom's macroglobulinemia patient. Mohammad, Ramzi M.; Aboukameel, Amro; Nabha, Sanaa; Ibrahim, Dina; Al-Katib, Ayad. Division of Hematology and Oncology, Department of Internal Medicine, Karmanos Cancer Institute, Wayne State University School of Medicine, Detroit, MI, USA. Journal of Drug Targeting (2002), 10(5), 405-410. Publisher: Taylor & Francis Ltd., CODEN: JDTAEH ISSN: 1061-186X. Journal written in English. CAN 138:198246 AN 2002:629464 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Waldenstrom's macroglobulinemia (WM) is an uncommon lymphoproliferative disease which remains incurable with current treatment protocols. A permanent WM cell line, WSU-WM, was previously established, which grows as a xenograft in severe combined immunodeficient (SCID) mice. This study investigated the antitumor effects of the rituximab (RTX), cyclophosphamide (CTX), dexamethasone (DEX) [RCD] regimen in vivo in mice with a WSU-WM SCID xenograft and in a patient with WM. For the preclin. efficacy study, WSU-WM-bearing SCID mice received RTX (150 mg/kg/injection i.v.), CTX (90 mg/kg/injection, s.c.) as single agents, or diluent. The combination group received RTX at 150 mg/kg/injection, CTX at 150 mg/kg/injection, and DEX at 1.0 mg/kg/injection, i.v. Tumor growth inhibition, tumor growth delay, and log10 kill (net) were 24.5%, 37 days, and 5.52 for RTX and 88%, 0.0 days, and 0.0 log10 kill for CTX. No cures were obsd. with either agent; however, all the mice (6/6) with bilateral tumors were cured when treated with the RCD regimen. A 57-yr-old patient with relapsed WM was treated with the RCD regimen and showed an excellent partial remission for 7 mo. The patient tolerated the treatment very well, the Hb improved dramatically, platelets remained stable, the IgM level normalized and there was only minimal involvement of bone marrow. Based on these results, the RCD regimen is effective against WM and should be further evaluated in clin. trials.

Answer 15:

Bibliographic Information

Potential mechanism for the effects of dexamethasone on growth of androgen-independent prostate cancer. Nishimura, Kazuo; Nonomura, Norio; Satoh, Eiichi; Harada, Yasunori; Nakayama, Masashi; Tokizane, Takashi; Fukui, Tatsunari; Ono, Yutaka; Inoue, Hitoshi; Shin, Masaru; Tsujimoto, Yuichi; Takayama, Hitoshi; Aozasa, Katsuyuki; Okuyama, Akihiko. Department of Urology, Graduate School of Medicine, Osaka University, Suita-City, Japan. Journal of the National Cancer Institute (2001), 93(22), 1739-1746. Publisher: Oxford University Press, CODEN: JNCIEQ ISSN: 0027-8874. Journal written in English. CAN 136:112930 AN 2001:926044 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Dexamethasone, a synthetic glucocorticoid, has clin. benefit in patients with hormone-refractory prostate cancer (HRPC), but the mechanisms responsible for its effects are unknown. The nuclear factor-κB (NF-κB)-dependent cytokine interleukin (IL) 6 (IL-6) is

thought to stimulate growth of HRPC. Because dexamethasone interferes with NF-κB activation, the authors detd. whether dexamethasone inhibits prostate cancer growth by working through the glucocorticoid receptor (GR) to interfere with NF-κB-IL-6 pathway. Three human prostate cancer cell lines (DU145, PC-3, and LNCaP) were assessed for GR expression and responsiveness to dexamethasone. Levels of GR, NF-κB, and the cytoplasmic NF-κB inhibitor IκBα were detd. by western blotting and of IL-6 by enzyme immunoassay. The subcellular localization of NF-κB was analyzed by immunofluorescence. The effects of dexamethasone (thrice weekly injections of 1 μg/mouse) on DU145 xenografts in nude and severe combined immunodeficient (SCID) mice were evaluated. GR expression in human prostate cancers was assessed by immunohistochem. All statistical tests were two-sided. Dexamethasone dose dependently decreased GR levels and inhibited the growth of DU145 and PC-3 but not LNCaP cells (DU145 cells, P<.001; PC-3 cells, P =.009). Dexamethasone increased IκBα protein levels and the cytosolic accumulation of NF-κB in DU145 cells and decreased secreted IL-6 levels to 37 pg/mL (95% confidence interval [CI] = 33 pg/mL to 41 pg/mL), compared with 164 pg/mL (95% CI = 162 pg/mL to 166 pg/mL) secreted by ethanol-treated control cells. Dexamethasone inhibited the growth of DU145 xenografts in nude (P =.006) and SCID (P =.026) mice without affecting GR levels. Eight of 16 human prostate cancers expressed GR at high levels (≥30% GR-pos. cells). Dexamethasone inhibited the growth of GR-pos. cancers, possibly through the disruption of the NF-κB-IL-6 pathway.